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Category of Case:
ACTH Secreting Pancreatic NET/Zollinger Elison Syndrome with Liver Metastasis

An 18-year-old girl with no past medical illness, presented with acute onset of Cushing's syndrome (CS), associated with weight loss, newly diagnosed diabetes and hypertension, and severe hypokalaemic metabolic alkalosis. Her early morning serum cortisol was 3600 nmol/l, overnight dexamethasone suppression test was 3421 nmol/l, and paired ACTH was high at 145.5 pmol/l. One week after admission, she developed upper gastrointestinal bleeding (UGIB) with OGDS revealed multiple Forrest 1B duodenal ulcers with pangastritis. Bleeders were secured and she was started with i.v Esomeprazole infusion. However, she had recurrent UGIB requiring multiple OGDS and blood transfusions which rendered her ICU admission and intubation for airway protection. An urgent CT abdomen revealed an enhancing pancreatic tail mass measuring 4.1x3.8x2.5cm, with liver metastasis, and bilateral adrenal gland hyperplasia. MRI pituitary was normal. Metastatic Neuroendocrine tumor (NET) or gastrinoma (Zollinger-Ellsion Syndrome (ZES)) with Ectopic ACTH Syndrome (EAS) was suspected. She was started on IV Etomidate, a cortisol inhibitor to reduce the cortisol level, and dose was titrated to maintain serum cortisol at 600-800 nmol/l, as well as oral Vonoprazan, a potassium-competitive acid blocker and high dose IV Esomeprazole to treat the refractory bleeding PUD. IV Octreotide infusion was also started as a treatment to both bleeding PUD and NET, and was later switched to S/C Octreotide LAR. A week later, she was started on oral Ketoconazole as an oral cortisol inhibitor to overlap with IV Etomidate. She was also started on IV hydrocortisone as block-and-replace therapy after the oral fluconazole titrated up to 1000mg a day. Bleeding was slowly stabilised after the double acid suppression therapy, Octreotide and by lowering down of serum cortisol. She subsequently had liver biopsy done showing NET grade 2. However, prolonged intubation and ICU stay had caused her to have severe nosocomial infections, complicated with Acute Respiratory Distress Syndrome, acute kidney injury and coagulopathy. Forty nine days after ICU admission, she had another round of UGIB that failed to be secured by OGDS. She then underwent laparotomy and under-running of the bleeding posterior duodenal Forrest 1A ulcer and biopsy of the pancreatic mass. Resection of the pancreatic tumor was not done as it would require total pancreatectomy which deemed to be futile in a case of metastatic disease. Patient finally succumbed on day 53 of ICU admission. Unfortunately, her pancreatic tumor biopsy failed to obtain representative tissue of the pancreatic tumor. Her genetic study was negative. This case highlights the aggressive nature of a case of Metastatic NET or ZES with EAS that failed to respond to various medical therapies.

Key Learning Points:

- Ectopic ACTH Syndrome (EAS) or dual hormone secretions is a rare manifestation of Pancreatic NET, and commonly associated with metastatic disease.
- Patients with sporadic ZES have more severe features of CS, rapid progression of disease and shorter median survival than those associated with MEN-1.
- EAS can present prior, concurrent or after the diagnosis of ZES/PNET.
- Common presentations: acute onset of CS, with severe weakness, weight loss, anorexia, severe hypokalaemia, sudden worsening of glycemic control in diabetic patients, and/or severe hyperpigmentation.
- Early recognition and diagnosis aid in initiating treatment promptly.
- Due to the aggressive nature of the disease, multidisciplinary team approach is needed.
- First-line treatment is surgery.
- Surgical removal of the PNET may not treat the CS successfully, other treatment modalities ie. medical therapy, PRRT, and/or adrenalectomy are often required.

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